PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 November 1998 (18.11.98)	
International application No. PCT/EP98/02138	**Applicant's or agent's file reference** VW/P31786
International filing date (day/month/year) 03 April 1998 (03.04.98)	**Priority date** (day/month/year) 05 April 1997 (05.04.97)
Applicant ULRICH, Jorj, Terry et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 November 1998 (02.11.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nicola Wolff
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

2342608

Copy for the Elected Office (EO/US)

PCT/EP98/02138

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WEST, Vivien
SmithKline Beecham plc
Corporate Intellectual Property
Two New Horizons Court
Brentford
Middlesex TW8 9EP
ROYAUME-UNI

Date of mailing (day/month/year)
15 December 1998 (15.12.98)

Applicant's or agent's file reference
VW/P31786

IMPORTANT NOTIFICATION

International application No.
PCT/EP98/02138

International filing date (day/month/year)
03 April 1998 (03.04.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
SMITHKLINE BEECHAM PLC
New Horizons Court
Brentford
Middlesex TW8 9EP
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
ALLERGY THERAPEUTICS LIMITED
7 Devonshire Square
Cutlers Gardens
London EC2M 4YH
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Athina Nickitas-Etienne
Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US) PCT/EP98/02138

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

MALLALIEU, Catherine, Louise
D. Young & CO.
21 New Fetter Lane
London EC4A 1DA
ROYAUME-UNI

Date of mailing (day/month/year) 21 January 1999 (21.01.99)	
Applicant's or agent's file reference VW/P31786	**IMPORTANT NOTIFICATION**
International application No. PCT/EP98/02138	**International filing date** (day/month/year) 03 April 1998 (03.04.98)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

WEST, Vivien
SmithKline Beecham plc
Corporate Intellectual Property
Two New Horizons Court
Brentford
Middlesex TW8 9EP
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 44 127 964 4399

Facsimile No.: 44 181 975 6294

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

MALLALIEU, Catherine, Louise
D. Young & CO.
21 New Fetter Lane
London EC4A 1DA
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 0171 353 4343

Facsimile No.: 0171 353 7777

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Athina Nickitas-Etienne Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002440487

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SMITHKLINE BEECHAM PLC
Corporate Intellectual Property
Attn. West, V.
Two New Horizons Court
Brentford
Middlesex TW8 9EP
UNITED KINGDOM

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference VW/P31786	Date of mailing *(day/month/year)* 13/08/1998 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 98/02138	International filing date *(day/month/year)* 03/04/1998
Applicant SMITHKLINE BEECHAM P.L.C. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Mike Iverstam

Form PCT/ISA/220 (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
VW/P31786		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 02138	03/04/1998	05/04/1997
Applicant		
SMITHKLINE BEECHAM P.L.C. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   [ ] filed with the international application.

   [ ] furnished by the applicant separately from the international application,

      [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

   [ ] Transcribed by this Authority

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant

   [X] the text has been established by this Authority to read as follows:

   ALLERGEN FORMULATION

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02138

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K39/39 //(A61K39/39,39:35),(A61K39/39,39:36)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 34626 A (SMITHKLINE BEECHAM) 7 November 1996 see the whole document	1-5
Y	GB 2 220 211 A (RIBI IMMUNOCHEM RESEARCH INC.) 4 January 1990 cited in the application see the whole document	1-5
Y	GB 1 492 973 A (BEECHAM) 23 November 1977 cited in the application see the whole document	1-5
Y	GB 1 377 074 A (BEECHAM) 11 December 1974 cited in the application see the whole document	1-5

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1998	13/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreau, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/02138

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9634626 A	07-11-1996	AU 5761696 A	21-11-1996
		CA 2217388 A	07-11-1996
		CN 1183046 A	27-05-1998
		CZ 9703429 A	18-03-1998
		EP 0825874 A	04-03-1998
		NO 974893 A	23-10-1997
		PL 323104 A	16-03-1998
GB 2220211 A	04-01-1990	US 4912094 A	27-03-1990
		CA 1317589 A	11-05-1993
		DE 3921416 A	04-01-1990
GB 1492973 A	23-11-1977	AU 7794375 A	05-08-1976
		BE 825579 A	14-08-1975
		DE 2505814 A	18-09-1975
		FR 2261013 A	12-09-1975
		JP 1222709 C	15-08-1984
		JP 50116626 A	12-09-1975
		JP 58022444 B	09-05-1983
		KE 3113 A	20-02-1981
		NL 7501582 A,B,	19-08-1975
		US 4070455 A	24-01-1978
		ZA 7500634 A	28-01-1976
GB 1377074 A	11-12-1974	AU 462878 B	10-07-1975
		AU 4450572 A	17-01-1974
		BE 786026 A	08-01-1973
		CA 973093 A	19-08-1975
		DE 2234474 A	25-01-1973
		DK 130455 B	24-02-1975
		FR 2145555 A	23-02-1973
		NL 7209574 A,B,	16-01-1973
		SE 385770 B	26-07-1976
		US 3792159 A	12-02-1974
		ZA 7204557 A	25-07-1973

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 39/39 // (A61K 39/39, 39:35)
(A61K 39/39, 39:36)

A1

(11) International Publication Number: WO 98/44947

(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number: PCT/EP98/02138

(22) International Filing Date: 3 April 1998 (03.04.98)

(30) Priority Data:
9706957.9 5 April 1997 (05.04.97) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ULRICH, Jorj, Terry [US/US]; Ribi Immunochem Research Inc., 553 Old Corvallis Road, Hamilton, MT 59840 (US). WHEELER, Alan, Worland [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ALLERGEN FORMULATION

(57) Abstract

A pharmaceutical composition comprising tyrosine, an optionally modified allergen, and 3–DMPL, is useful in the prevention and treatment of allergy.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02138

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K39/39 //(A61K39/39,39:35),(A61K39/39,39:36)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 34626 A (SMITHKLINE BEECHAM) 7 November 1996 see the whole document	1-5
Y	GB 2 220 211 A (RIBI IMMUNOCHEM RESEARCH INC.) 4 January 1990 cited in the application see the whole document	1-5
Y	GB 1 492 973 A (BEECHAM) 23 November 1977 cited in the application see the whole document	1-5
Y	GB 1 377 074 A (BEECHAM) 11 December 1974 cited in the application see the whole document	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1998	13/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreau, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/02138

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9634626 A	07-11-1996	AU 5761696 A	21-11-1996
		CA 2217388 A	07-11-1996
		CN 1183046 A	27-05-1998
		CZ 9703429 A	18-03-1998
		EP 0825874 A	04-03-1998
		NO 974893 A	23-10-1997
		PL 323104 A	16-03-1998
GB 2220211 A	04-01-1990	US 4912094 A	27-03-1990
		CA 1317589 A	11-05-1993
		DE 3921416 A	04-01-1990
GB 1492973 A	23-11-1977	AU 7794375 A	05-08-1976
		BE 825579 A	14-08-1975
		DE 2505814 A	18-09-1975
		FR 2261013 A	12-09-1975
		JP 1222709 C	15-08-1984
		JP 50116626 A	12-09-1975
		JP 58022444 B	09-05-1983
		KE 3113 A	20-02-1981
		NL 7501582 A,B,	19-08-1975
		US 4070455 A	24-01-1978
		ZA 7500634 A	28-01-1976
GB 1377074 A	11-12-1974	AU 462878 B	10-07-1975
		AU 4450572 A	17-01-1974
		BE 786026 A	08-01-1973
		CA 973093 A	19-08-1975
		DE 2234474 A	25-01-1973
		DK 130455 B	24-02-1975
		FR 2145555 A	23-02-1973
		NL 7209574 A,B,	16-01-1973
		SE 385770 B	26-07-1976
		US 3792159 A	12-02-1974
		ZA 7204557 A	25-07-1973

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 39/39 // (A61K 39/39, 39:35)
(A61K 39/39, 39:36)

A1

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(57) Abstract

A pharmaceutical composition comprising tyrosine, an optionally modified allergen, and 3–DMPL, is useful in the prevention and treatment of allergy.

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ALLERGEN FORMULATION

This invention relates to novel formulations for use in desensitisation therapy of allergy sufferers.

It is known that desensitisation therapy results in a changed immunological response specific for the allergens administered. Such changes are considered to be responsible for the beneficial effects of the treatment and amelioration of the symptoms of allergy.

The immunological changes responsible for benefit are not entirely understood. Although a raised allergen specific IgG antibody response is considered to be a desirable outcome of therapy, it is now believed that certain changes in the allergen specific T cell (T lymphocyte) response are more important.

Two subclasses of T cell, TH1-like and TH2-like interact with one another via various messenger molecules. In an allergic subject it appears that there is a greater allergen specific TH2 than a TH1 activity. This can lead to a high allergen specific IgE antibody level and greater eosinophil activity. These are two important components of the allergic syndrome.

A change in the above situation to one where there is greater allergen specific TH1 rather than TH2 activity is thought to be an important component of immunotherapy leading to a clinical benefit.

GB-A-1 377 074 describes a process for preparing coprecipitates of tyrosine having an allergen dispersed therein.

GB-A-1 492 973 describes a process for preparing coprecipitates of tyrosine having a modified allergen dispersed therein. The allergen has been modified by treatment with an agent, such as glutaraldehyde, which causes intra-molecular cross-linking and reduces the allergenicity of the product relative to the unmodified allergen.

3 De-O-acylated monophosphoryl lipid A (hereinafter 3-DMPL or "MPL") is known from GB 2220211 (Ribi). Chemically it is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem Montana. A preferred form of 3 De-O-acylated monophosphoryl lipid A is disclosed in International Patent Application No. 92/116556. 3-DMPL is an example of a substance that can enhance the TH1 over TH2 directing properties of administered allergens.

According to the present invention there is provided a pharmaceutical composition comprising tyrosine, an optionally modified allergen, and 3-DMPL. Typically, the allergen is coated with and /or adsorbed onto tyrosine, for example by co-precipitation or mixing.

The 3-DMPL can be mixed with the other components of the composition prior to administration. Alternatively it can be formulated together with the other components during manufacture of the product. Alternatively, it can be administered at a different site or time

than the other components. Administration can be by a number of routes including parenteral and enteral.

A further aspect of the invention thus provides a method of treating a patient who is susceptible to allergy, which method comprises administering to the said patient an effective amount of tyrosine, an optionally modified allergen, and 3-DMPL.

A further aspect of the invention provides use of tyrosine, an optionally modified allergen, and 3-DMPL, in the preparation of a medicament for use in the prevention or treatment of allergy.

The allergen may be derived from any allergy causing substance, such as a pollen (e.g. ragweed or birch pollen), food, insect venom, mould, animal fur, or house dust mite (*D. farinae* or *D. pteronyssinus*). As used herein, "allergen" includes a mixture of allergens which may be from a single source or more than one source. The term "allergen" also includes peptides containing one or more epitopes of an allergen, such as allergen fragments, prepared by total synthesis, by enzymatic degradation of allergens, or by other means.

The allergen is optionally modified by reaction with a cross-linking agent such as a dialdehyde, more particularly glutaraldehyde.

A further aspect of the invention provides a process for the preparation of a pharmaceutical composition in accordance with the invention, which process comprises (a) (optionally) modifying an allergen by reaction with a cross-linking agent, (b) mixing an aqueous solution of the optionally modified allergen with a solution of tyrosine in a strong aqueous acid, (c) neutralising the mixture of solutions, thereby co-precipitating tyrosine and modified allergen, (d) mixing the product with 3-DMPL, and (e) optionally, adding a physiologically acceptable carrier.

Suitable physiologically acceptable carriers include phenol-saline and sterile water.

Typically, the allergen is modified by treatment with a dialdehyde such as glutaraldehyde, in aqueous solution at a pH of between 5 and 10, typically about 7, and a temperature of between 0 and 100 °C, more usually between 4 and 37 °C, for up to 10 hours, for example about two hours at room temperature. The ratio of allergen to glutaraldehyde is typically in the range 50:1 to 2:1, for example about 10:1.

The intermediate can be freeze dried or used in the next stage.

A solution of the modified allergen, typically at pH 7±1, obtained either as the reaction mixture from the cross-linking process or from the solvation of a solid, is then mixed with a solution of tyrosine in a strong aqueous acid. The strong acid is usually an inorganic acid, preferably hydrochloric acid. The solution of allergen used in this step typically contains between 0.1 µg/ml and 1000 µg/ml allergen protein, for example about 400µg/ml. The ratio of allergen: tyrosine in the mixture is typically in the range $1:4 \times 10^5$ to $1:1 \times 10^2$ w/w.

The resulting mixture of solutions of allergen and tyrosine is neutralised. By neutralisation is meant an adjustment of pH to a value within the range 4.0 to 7.5. It is important that, at no time, or at least at no prolonged time, during the neutralisation does the pH of the solution rise appreciably above 7.5. This condition can be met by vigorous stirring of the solution and by the use only of the required amount of base, if desired. Various buffering agents can usefully be added to the solutions of allergen to assist in pH control during the mixing and neutralising stages.

A particularly useful method of carrying out the neutralisation is for separate streams of the solution of tyrosine in acid and the neutralising base to be run into the solution of allergen. The rates of flow of the added solutions are controlled by pH-state, that is by equipment which regulates the flow of one or both of the solutions so that the pH of the reaction mixture remains substantially constant at a predetermined level. We have found that optimum results are usually obtained by pH control within the range 6.5 to 7.5 though the precise pH may vary according to the nature of the allergen.

The result of the neutralisation is the immediate precipitation of the tyrosine, within and/or upon which the solution of allergen is occluded and/or adsorbed. After the precipitation the mixture is either washed immediately or allowed to stand for a period of from a few hours to a day or two prior to washing.

The resulting precipitate may be removed from the solution by centrifugation or filtration and washed, e.g. with phenol-saline, before being resuspended in a physiologically-acceptable carrier such as phenol-saline, or sterile water, to produce an injectable composition suitable for use in desensitisation therapy in combination with 3-DMPL.

MPL which has been dissolved by the method described in Preparation 3 below or by sonication can be diluted by various means prior to its addition to tyrosine adsorbates of allergens or modifed allergens. The preparation of MPL is initially made at a concentration of typically between 0.5mg per ml and 4 mg per ml, for example 1 mg per ml. It can then be diluted to a concentration of between 500 µg per ml and 20 µg per ml, preferably about 100 µg per ml. This dilution can be made in pure water, or in an aqueous glycerol solution containing between 1% and 4 %, preferably 2 %, glycerol. Such dilutions can then be added to a suspension of the tyrosine adsorbate prepared as described above. For convenience, the concentration of the MPL solution and the tyrosine adsorbate suspension respectively may be selected such that approximately equal volumes of each are admixed to obtain the final product for injection. A typical final product contains about 100µg per ml of allergen and about 250µg per ml of MPL.

The following Example illustrates the present invention:

Preparation 1

A neutral solution of approximately 0.5 mg/ml grass pollen extract which had been partially purified by dialysis or fractionation was chemically modified by the addition of an equal volume of 0.25% w/v glutaraldehyde and the mixture stirred for approximately 2 hours at room temperature. To the above mixture was added phosphate buffer solution at a pH of 7 ±1. The allergen solution was co-precipitated with tyrosine by the simultaneous addition of one volume of L-tyrosine in HCl (prepared by dissolving 24g L-tyrosine to 100ml with 3.8M HCl) and one volume of 3.2M NaOH, to four volumes of allergen solution, with vigorous agitation. The suspension so formed was centrifuged, washed repeatedly with buffered saline to remove contaminants and resuspended to the original volume in buffered saline pH6 ±1.

3-DMPL suitable for coadministration with the above formulation was prepared as described in Preparation 3 below.

Preparation 2

Eight mg of ovalbumin (XOA) were dissolved by mixing in 20ml of EVANS solution. Next 6.9ml of phosphate buffer were added with mixing. The solution was placed in a 100ml beaker containing a magnetic stir bar. While mixing using a magnetic stirrer, 6.9ml of 3.2N NaOH and 6.9ml of 3.8N HCL containing 24% W/V-tyrosine were added simultaneously, dropwise, over a period of 5 min. to form a precipitate. The mixture was allowed to stir for an additional 5 min. and then transferred to a 50ml centrifuge tube and centrifuged for 10 min. at 2500 rpm. After centrifugation the supernatant was decanted and the pelleted precipitate resuspended in 40ml of phosphate buffer. The mixture was centrifuged for 5 min. at 2500 rpm. After centrifugation the supernatant was decanted and the precipitate resuspended in 40ml of phosphate buffer. The mixture was centrifuged for 5 min. at 2500 rpm. After centrifugation the supernatant was decanted and the pelleted precipitate resuspended in 40ml of phosphate buffer saline, pH7.2, containing 0.4% V/V glycerol and 0.01% W/V thimerosal as a preservative. The final product contained approximately 40mg/ml of tyrosine adsorbate. Assuming 100% binding of the XOA to the tyrosine adsorbate the XAO was at 200µg/ml in the final product. The XOA-tyrosine adsorbate was stored at 4°C until needed.

Preparation 3

A 4 mg/ml solution of 1,2-dipalmitoyl-SN-glycero-3-phospho choline (DPPC) in absolute ethanol was prepared. For each 1.0mg of MPL®-TEA salt to be solubilized, 27µl of DPPC were added to dissolve the MPL®. The ethanol was removed by blowing a stream of N_2 gently into the vial. Next 1.0ml of pyrogen-free water for injection was added for each mg of MPL® in the dried MPL® /DPPC mixture. The solution was sonicated in a bath sonicator at 60-70°C until clear. The MPL®/DPPC solution was then filter sterilized by filtration through a SFCA 290-4520 Nalgene 0.2µm filter. The MPL®/DPPC solution was aseptically dispensed at 1.0mg/ml into depyrogenated vials, labelled MPL®-AF, and stored at 4°C.

Biological activity

TH1 inducing activity in mice can be equated with the production of IgG2a and IgG2b antibodies and the TH2 inducing activity with the production of IgG1 antibodies and IgE antibodies.

Therefore, as an example, an experiment was carried out in mice to demonstrate the profiles of the allergen specific antibodies to an exemplar allergen ovalbumen (XOA) which is a well-known food allergen derived from chicken eggs. It was confirmed that a formulation consisting of MPL + XOA+tyrosine stimulated a more advantageous antibody profile than MPL + XOA, XOA+tyrosine or XOA alone.

Groups of 8 BALB/c female mice, 6-8 weeks of age, were injected subcutaneously in the inguinal area with 0.2ml of one of the following vaccines:

XOA+Tyrosine: The XOA tyrosine adsorbate prepared in Preparation 2 above was diluted with an equal volume of phosphate buffered saline within 30 min. prior to injection.

XOA+Tyrosine+MPL: The XOA tyrosine adsorbate prepared in Preparation 2 above was diluted with an equal volume of MPL®-AF at 500µg/ml in phosphate buffered saline within 30 min. prior to injection.

XOA+MPL: XOA was dissolved in phosphate buffered saline at 200µg/ml and diluted with an equal volume of MPL®-AF at 500µg/ml in phosphate buffered saline within 30 min. prior to injection.

XOA Alone: XOA was dissolved at 200µg/ml in phosphate buffered saline and diluted with an equal volume of phosphate buffered saline.

Twenty-one days later the four groups of mice were boosted with 0.2ml of freshly prepared vaccines. Fourteen days following the booster the mice were bled and the sera separated and stored at -70°C until assay.

The sera were assayed by conventional ELISA technique using horseradish conjugated goat anti-mouse IgG_1, IgG_{2a}, and IgG_{2b} antibodies purchased from Southern Biotechnology, Inc. (Birmingham, AL) and used according to the manufacturer's instruction. The IgG_1, IgG_{2a}, and IgG_{2b} titers represent the reciprocal serum dilution giving a reading of >0.1 OD units at A_{490}. The serum IgE levels were measured using an anti-IgE capture ELISA followed by the use of a biotinylated ovalbumin probe. Binding was measured following the addition of a horseradish conjugated strepavidin preparation. The results are reported as OD units at A_{490}.

RESULTS

Formulation	IgG1 titre	IgG2a titre	IgG2b titre	IgE OD at 1/10 Dilln
OVA + Tyrosine	102400	100	200	0.213
OVA+Tyrosine +MPL	409600	102400	102400	0.104
OVA + MPL	102400	200	400	0.218
OVA alone	6400	<100	<100	0.235
Normal Mouse Serum Values	<100	<100	<100	0.095

Of particular importance is the fact that the combination of allergen + tyrosine + MPL induces less allergen specific IgE antibody than the other combinations. Furthermore, the ratio of IgG2a or IgG2b to IgG1 antibodies is greater and consistent with the highest levels of the two former antibody isotypes seen in the experiment in the mice given allergen+tyrosine+MPL than in any other group of mice. This is indicative of a better ratio of TH1 cell induction over TH2 cell induction in this group compared with that induced in the other groups of mice.

Claims

1. A pharmaceutical composition comprising tyrosine, an optionally modified allergen, and 3-DMPL.

2. A composition according to claim 1, wherein the allergen is coated with and /or adsorbed onto tyrosine.

3. A method of treating a patient who is susceptible to allergy, which method comprises administering to the said patient an effective amount of tyrosine, an optionally modified allergen, and 3-DMPL.

4. Use of tyrosine, an optionally modified allergen, and 3-DMPL, in the preparation of a medicament for use in the prevention or treatment of allergy.

5. A process for the preparation of a pharmaceutical composition according to claim 1 or 2, which process comprises (a) (optionally) modifying an allergen by reaction with a cross-linking agent, (b) mixing an aqueous solution of the optionally modified allergen with a solution of tyrosine in a strong aqueous acid, (c) neutralising the mixture of solutions, thereby co-precipitating tyrosine and modified allergen, (d) mixing the product with 3-DMPL, and (e) optionally, adding a physiologically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Ir ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K39/39 //(A61K39/39,39:35),(A61K39/39,39:36)

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 34626 A (SMITHKLINE BEECHAM) 7 November 1996 see the whole document	1-5
Y	GB 2 220 211 A (RIBI IMMUNOCHEM RESEARCH INC.) 4 January 1990 cited in the application see the whole document	1-5
Y	GB 1 492 973 A (BEECHAM) 23 November 1977 cited in the application see the whole document	1-5
Y	GB 1 377 074 A (BEECHAM) 11 December 1974 cited in the application see the whole document	1-5

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP 98/ 02138	03/04/1998	05/04/1997
Applicant		
SMITHKLINE BEECHAM P.L.C. et al.		

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   ALLERGEN FORMULATION

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1998	13/08/1998

Name and mailing address of the ISA	Authorized officer
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